and joined claim 35 of Group III. Therefore, claims 1-12, 16-22, 29-31, 32, 34, 35 and 38 are pending and under examination. As noted by the Examiner, Applicants request that once allowable product claims are indicated, the method claims of Groups IV-VI that are limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

1. Priority

Applicants have amended the specification to state the priority claim as requested by the examiner.

2. Drawings

Applicants will attend to drawing corrections in accordance with form PTO-948 when allowable subject matter is indicated by the Examiner.

3. Specification

The Examiner has objected to the specification because the brief description of the figures on pages 17 and 18 lacks a separate brief description for Figures 4A-C and Figures 5A-B. In regard to Figures 4, "(A-C)" on page 17, in the third line of the description of the figures, Fig. 4 recites that (A-C) shows the primary cultures of bone marrow from three individual patients with prostate cancer. It is believed that this description is clear in describing Fig. 4 A-C. Applicants believe that this recitation is sufficient to indicate that these three figures represent the data from the three patients.

In regard to Figures 5A and 5B, the brief description of the drawings has been amended to include text from Example 9. It is believed that this should overcome the Examiner's objections, and it is requested that these objections be withdrawn.

4. Rejection under 35 U.S. C. § 112, first paragraph

Claims 33-35 are rejected as not being enabled for "a pharmaceutical composition comprising the epithelial tumor cell." The Examiner acknowledges that the specification is enabled for a composition comprising an epithelial tumor cell of claim 1 and a pharmaceutically acceptable carrier. Although Applicants do not agree with the

Examiner's basis for this rejection, claims 33 and 34 have been amended to claim a composition of epithelial tumor cells, optionally in combination, with a pharmaceutically acceptable carrier, but wish to point out that on pages 14 and 15 of the specification as filed, it is clearly described that the pharmaceutical composition which comprises the inventive epithelial tumor cell may be used for the prophylaxis of cancer and, employed as vaccines. It is requested that this rejection be withdrawn.

5. Rejection under 35 U.S. C. § 112, second paragraph

The Examiner rejects claims 7, 12, 29 and 33-35 as being indefinite. Claims 7 and 12 are considered to be vague and indefinite in the recitation of "replication deficiency" and "B7," respectively.

The term "replication deficiency" is clearly defined in the specification beginning on page 8, third complete paragraph to page 9, through the first complete paragraph. It is clear from this explanation that the term "replication deficiency" is the deficiency or mutation in the SV40 virus that does not allow it to be replicated or unwound.

The term "B7" is defined on page 10, last paragraph, lines 8 to 14 of the application as filed, and relates to a co-stimulatory factor known by the person skilled in the art at the priority date of this application. This portion of the specification cites Guinan *et al.*, *Blood* 84: 326-328, (1994), (copy will be provided) wherein the term "B7" is clearly defined.

In view of these arguments and amendments to the claims, it is requested that these rejections be withdrawn.

6. Rejection under 35 U.S. C. § 102

The Examiner is rejects claims 1-3, 6-10, 16-19, 21 and 22 as being anticipated by Garcia *et al* ("Garcia"). Garcia, in the Examiner's opinion, discloses autologous, disseminated immortalized rabbit mammary epithelial tumor cells containing a oncogene. However, Garcia actually discloses an immortalized epithelial cell, which after transformation was tumorigenic, but had no metastatic potential. Furthermore, the transformed original cell was a primary rabbit mammary secretory cell, i.e., a normal tissue cell and not a tumor cell as recited in claim 1 of the present application. Garcia

discloses on page 1974, right-hand column, last two sentences to page 1975, left-hand column, first two lines that to transform primary cells, these cells were obtained from rabbit mammary epithelial cells from rabbits in mid-pregnancy (in this context Garcia cites Kraehenbuhl, *Journal of Cell Biol.*, 72: 390-405 (1977) (copy will be provided). From the above mentioned citation of Garcia and from Kraehenbuhl, it is evident that the cells are normal mammary cells from rabbits and not tumor cells. Therefore, Garcia describes the transformation of normal epithelial cells and not of tumor cells. For all of the reasons set forth above, it is requested that this rejection be withdrawn.

7. Rejection under 35 U.S. C. § 103

7.1 Claims 1, 4, 5, and 16-20

Claims 1, 4, 5 and 16-20 are alleged to be obvious over Garcia in view of Schlimok *et al.* ("Schlimok") and Yanagihara *et al.* ("Yanagihara"). The Examiner applies Garcia as above, and states that Garcia does not teach the epithelial tumor cell of claim 1;, i.e., a human non-immortalized tumor cell derived from body fluid, such as bone marrow. The Examiner applies Schlimok to teach the detection of human epithelial tumor cells in bone marrow aspirates using monoclonal antibodies (mAbs) to cytokertin polypeptide #18, specific for cells of the epithelia. The Examiner concludes that one would have been motivated to combine these two disclosures to detect the claimed tumor cells in bone marrow aspirates. Then, the Examiner cites Yangihara as teaching the introduction of an oncogene into a cell to elucidate the role of oncogenes in the metastatic process. The Examiner alleges that one would have been motivated to introduce an oncogene into the cell line to monitor metastatic ability of the oncogene-bearing cells, Schlimok's process could be used to detect such tumor cells for monitoring and recognizing cancer status to monitor the effectiveness of therapies.

Applicants respectfully disagree with the Examiner's basis for this hindsight reconstruction rejection. Firstly, Garcia is not applicable for all of the reasons set forth above because Garcia does not disclose the transformation of a tumor cell but rather Garcia describes the transformation of a normal epithelial cell, and therefore the immortalization of a non-tumor cell. Furthermore, Garcia discloses the transformation of a rabbit cell by micro-injecting SV40 viral DNA and/or the human oncogen Ha-ras. In

this regard, Garcia stresses on page 1980, left-hand column, first paragraph of discussion, second and third paragraphs:

"When injected alone, these molecules were unable to transform rabbit mammary cells. The combination of SV40 DNA and activated c-Ha-ras gene, however, induced drastic changes in the micro-injected cells" (emphasis added)

In addition, on page 1974, right-hand column, last sentence of the introduction, Garcia points out:

"An immortalized cell line obtained after injecting SV40 DNA into primary cells retained some but not all of the differentiation markers of mammary secretory cells from pregnant rabbits, whereas a cell line fully transformed by SV40 and the activated human c-Ha-ras DNA became tumorigenic." (emphasis added)

Therefore, Garcia teaches that tumorigenic cells can be obtained form normal epithelial cells by co-injecting SV40 and the human oncogene c-Ha-ras.

Garcia employs cytokeratin staining in order to identify cells of epithelial origin in bone marrow. However, the staining procedure as outlined on page 832 of Schlimok uses glutaraldehyde fixation. The identified cells are, therefore, not viable and can certainly not be used according to the present invention. Therefore, there is no motivation to combine Schlimok with Garcia if Schlimok's method would result in non-viable cells.

Further, the Examiner states that Yanagihara teaches the artificial preparation of a tumor cell line by in vivo γ-radiation of a tumor in a mouse (see "material and methods", page 348, "Establishment culture of mouse tumor line"). From this radiated tumor Yanagihara isolated the cell line OV3121 which does not comprise any metastatic potential (see page 347, right-hand column, second paragraph, first sentence). Then, this non-metastatic epithelial tumor cell line was transfected with various oncogenses, in order to identify oncogenses which are capable of inducing metastatic changes in cells. In contrast to Yanagihara, the present application describes the introduction of an oncogene for immortalization, and thereby the preparation of an immortalized cell line. The preparation of the present immortalized cell line is based on a completely different mechanism/technique than the corresponding disclosure in Yanagihara, and as such provides no motivation to combine these teachings.

In regard to the method of producing tumor cells, a further difference between Yanagihara and the present invention is the present invention describes the

immortalization of a single cell which had been isolated from human tumor tissue. In contrast, Yanagihara isolated immortalized cells after a whole tumor had been radiated, and different cells had been isolated, in order to screen *in vitro* for a cell line that can be propagated in culture.

Applicants respectfully disagree with the Examiner's rationale for combining the cited prior art. The Examiner has utilized impermissible hindsight to construct the present rejection based upon Applicants' own disclosure. Applicants respectfully point out that the Examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining elements to make out a *prima facie* case of obviousness, the Examiner is obliged to show by reference to specific evidence in the cited references that there was (i) a suggestion to make the combination and (ii) a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The Examiner has failed to support the alleged case of *prima facie* obviousness, and as a result of these deficiencies, it is requested that this rejection be withdrawn.

Obviousness "'cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination.'" *In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988), *citing ACS Hosp. Sys. v. Montefiore Hosp.*, 221 USPQ 929, 933 (Fed. Cir. 1984). It is applicants' position that the combination of the prior art fails to provide a suggestion to make the present invention, and this rejection should be withdrawn.

7.2 Claims 1, 11, 12, 16, 29 and 30

Claims 1, 11, 12, 16, 29 and 30 are alleged to be obvious over Garcia in view of Blankenstein *et al.* ("Blankenstein"). The Examiner applies Garcia as above, and again, it is stressed that Garcia transforms normal epithelial cells. Further Garcia does not disclosing an epithelial tumor cells having integrated in its genome or another replicative genetic element as an externally introduced gene encoding a cytokine immunostimulatory factor, such as IL-4. However, the Examiner alleges that Blankenstein teaches the transfer of single cytokine genes into cancer cells. The Examiner then alleges that one

would have been motivated to do so because the expression of immunostimulatory factors in cancer cells would mediate powerful tumor suppression potential in T-cell deficient animals. The Examiner further states that Blankenstein suggests that cancer cells that produce certain cytokines might induce effective tumor-specific immunity in cancer patients.

Applicants disagree with the Examiner's characterization of Blankenstein because Blankenstein merely reviews the use of cytokines in cancer treatment and their potential role in tumor suppression by local delivery of cytokines through gene transfer. Again, the person skilled in the art would not have combined this reference with Garcia in order to arrive at the claimed subject matter. As argued above, Garcia does not teach the cells of claim 1, and there is no motivation within the prior art cited to suggest Applicants' claimed invention. It is requested that this rejection be withdrawn.

7.3 Claims 1, 16-19, 21 and 31

Claims 1, 11, 12, 16, 29 and 30 are alleged to be obvious over Garcia in view of THE Signma Cell Culture Catalogue and Price List ("Sigma"). The Examiner applies Garcia as above, and further states that Garcia discloses the production of tumor cells in medium containing EGF but not containing recombinant EGF, basic FGF or recombinant human basic FGF. The Examiner then states that Sigma, however, teaches the availability of these factor supplements. The Examiner concludes that it would be obvious to combine the teachings of Garcia and Sigma to obtain the claimed invention. As argued above, claim 1 is not anticipated by Garcia's disclosure nor is it obvious over Garcia. Sigma does not cure this deficiency. The subject matter of claims 1, 16-19, 21 and 31 are not obvious, and it is requested that this rejection be withdrawn in view of the arguments presented above regarding the novelty and nonobviousness of Garcia.

7.4 Claims 1, 33 and 34

Claims 1, 33 and 34 are alleged to be obvious over Garcia in view of Gottlinger *et al.* ("Gottlinger"). The Examiner applies Garcia as above, and again, it has to be stressed that Garcia transforms normal epithelial cells not tumor cells. The Examiner states that Garcia does not teach a composition comprising the epithelial tumor cell nor when the composition is a vaccine. Gottlinger is applied to teach compositions containing

epithelial cell surface antigens and *Bordetella pertussis* adjuvant suitable for mounting an immunological response. However, Goettlinger uses fresh colon tumor material from a metastasis to immunize mice for the production of a novel anti-EpCAM monocional antibodies, and not cells even remotely similar to those of Garcia. But the Examiner states that it would be obvious to combine the teach of Garcia and Gottlinger to generate antibodies. Again there is no motivation within the prior art to combine these references and the Examiner utilizes impermissible hindsight as the basis to do so. In view of these arguments and the arguments made above supporting the novelty and nonobviousness of Garcia, and the case law supporting nonobviousness of the present invention, it is requested that this rejection be withdrawn.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they solicit an early indication to that effect. Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, a telephone call to the undersigned, at the telephone number listed below, is courteously invited.

Respectfully submitted,

May 17, 2000
Date

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